Supra-treatment threshold neonatal jaundice: Incidence in HIV-exposed compared to non-exposed neonates at Queen Elizabeth Central Hospital in Blantyre, Malawi

W Nakanga, P Patel, S Panjwani, N Kennedy, K Kawaza

Department of Paediatrics & Child Health, College of Medicine, University of Malawi, Blantyre, Malawi

Correspondence to: Wisdom Nakanga
E-mail: wisdomnakanga@gmail.com

Abstract

Introduction
Jaundice is the yellowish pigmentation of the skin, sclera, and mucous membranes resulting from bilirubin deposition. Children born to mothers with HIV are more likely to be born premature, with low birth weight, and to become septic—all risk factors for neonatal jaundice. Further, there has been a change in the prevention of mother-to-child transmission (PMTCT) of HIV guidelines from single-dose nevirapine to a six-week course, all of which theoretically put HIV-exposed newborns at greater risk of developing neonatal jaundice.

Aim
We carried out a study to determine the incidence of severe and clinical neonatal jaundice in HIV-exposed neonates admitted to the Chatinkha Nursery (CN) neonatal unit at Queen Elizabeth Central Hospital (QECH) in Blantyre.

Methods
Over a period of four weeks, the incidence among non-exposed neonates was also determined for comparison between the two groups of infants. Clinical jaundice was defined as transcutaneous bilirubin levels greater than 5 mg/dL and severe jaundice as bilirubin levels above the age-specific treatment threshold according the QECH guidelines. Case notes of babies admitted were retrieved and information on birth date, gestational age, birth weight, HIV status of mother, type of feeding, mode of delivery, VDRL status of mother, serum bilirubin, duration of stay in CN, and outcome were extracted.

Results
Of the 149 neonates who were recruited, 17 (11.4%) were HIV-exposed. One (5.88%) of the 17 HIV-exposed and 19 (14.4%) of 132 HIV-non-exposed infants developed severe jaundice requiring therapeutic intervention ($p = 0.378$). Eight (47%) of the HIV-exposed and 107 (81%) of the non-exposed neonates had clinical jaundice of bilirubin levels greater than 5 mg/dL ($p < 0.001$).

Conclusions
The study showed a significant difference in the incidence of clinical jaundice between the HIV-exposed and HIV-non-exposed neonates. Contrary to our hypothesis, however, the incidence was greater in HIV-non-exposed than in HIV-exposed infants.

Introduction

Jaundice is the yellowish pigmentation of the skin, sclera and mucous membranes.[1] The yellow colour results from the accumulation of bilirubin pigment in the skin.[2] Neonatal jaundice or neonatal hyperbilirubinaemia refers to jaundice that is present at birth or appears at any time during the neonatal period.[2] In neonates, hyperbilirubinaemia is detected when the serum bilirubin levels become greater than 5 mg/dL and is termed clinical jaundice.[3] Jaundice can be physiological or pathological.[4]

Physiological jaundice is a common problem in term and preterm infants during the first week after birth and is the result of increased bilirubin production from the breakdown of foetal red blood cells combined with transient limitations in the conjugation of bilirubin by the immature neonatal liver.[2] For most of these infants, jaundice is mild and resolves without treatment. More than 50% of normal newborn, and 80% of preterm infants, have some jaundice.[5]

A small group of infants develop pathological jaundice. This may be an exaggeration of normal physiologic processes or may be an indicator of underlying disorders.[6] Pathological jaundice usually appears in the first 24 hours or after the first week of life, and the list of differential diagnoses include haemorrhage, sepsis, and congenital infections, such as toxoplasmosis, rubella, cytomegalovirus, herpes, and syphilis.[2]

Risk factors of neonatal jaundice include low birth weight, prematurity, ABO incompatibility, and sepsis.[3] In Malawi, 10% of neonates are born to HIV seroreactive mothers.[9] Several studies have found very high rates of prematurity, low birth weight, and very low birth weight (all risk factors for neonatal jaundice) in the infants of HIV-positive mothers.[8,9] In addition, other perinatal infections that predispose neonates to jaundice, such as hepatitis B and C, syphilis, toxoplasmosis, cytomegalovirus, herpes simplex virus, and tuberculosis exhibit high co-morbidity with HIV.[10] Nevirapine has been known to cause hepatic inflammation and therefore is associated with increased levels of serum bilirubin.[10,11] The new prevention of mother-to-child transmission (PMTCT) guidelines from single-dose nevirapine prophylaxis to a six-week course in newborns,[10] means that, in theory, the risk of developing clinical jaundice in HIV-exposed neonates is increased.

Non-invasive techniques for bilirubin measurement that correlate with serum bilirubin levels, such as with the use of a transcutaneous bilirubinometer, may be used to screen infants, but determination of serum bilirubin level is indicated in patients with elevated age-specific transcutaneous measurement, progressing jaundice, or risk for either haemolysis or sepsis.[2] Severe jaundice is defined as clinical jaundice and serum bilirubin levels above treatment threshold levels for gestational age and postpartum age. If the bilirubin level is greater than the threshold value, the neonate is started on phototherapy.[12] The levels of bilirubin, which are determined as supra-threshold and require treatment, are different according to the days of life and whether the neonate is healthy or preterm, as summarized in Table 1.[12]

Table 1: Treatment thresholds for neonatal jaundice depending on day of life and clinical status of neonate[12]

Day of life	Healthy term baby (mg/dL)	Preterm, low birth weight, sick (mg/dL)
Day 1	Treat any visible jaundice with phototherapy	Treat any visible jaundice with phototherapy
Day 2	15	13
Day 3	18	16
Day 4 and after	20	17

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Jaundice—if untreated or if treatment thereof is delayed—can lead to significant neurological sequelae. These include movement disorders like athetoid cerebral palsy and dystonia, auditory dysfunction, auditory neuropathy (ANSD), oculomotor impairments (nystagmus, strabismus, impaired upward or downward gaze, and/or cortical visual impairment) and other disorders such as dental enamel hypoplasia/dysplasia of the deciduous teeth, gastroesophageal reflux, and impaired digestive function.[2]

While there is a correlation between the risk factors for neonates to become jaundiced and the risks and co-morbidities that HIV-exposed neonates face, few studies have compared the incidence of neonatal jaundice between HIV-exposed and HIV-non-exposed neonates. The hypothesis of this study was that the incidence of jaundice may be higher in HIV-exposed neonates than in HIV-non-exposed neonates.

Methods

Study population, sample size, and study setting

This prospective cohort study was conducted at the Gogo Chatinkha Nursery (CN) neonatal unit at Queen Elizabeth Central Hospital over a four-week period. The admission criteria for CN includes those neonates who are premature, of low birth weight, or are exibiting any danger signs in a neonate, for example, dyspnoea or poor colour. The study population comprised neonates admitted to CN. Only neonates who met the inclusion criteria were included in the study after consent was obtained from their mothers.

The inclusion criteria were that newborn babies had to be free from jaundice and admitted to CN. The following were not eligible for the study: neonates who already had jaundice, neonates with significant congenital anomalies, and neonates of mothers whose HIV statuses were not known.

The study participants were recruited using stratified sampling. Two groups of eligible neonates whose mothers were HIV-positive and HIV-negative were identified. A random sample of 69 babies was drawn from each group. The calculated sample size of 138 (69 exposed and 69 non-exposed) babies was generated using Epi info version 3.5, with a confidence level of 90%, power of 80%, exposed to non exposed-ratio of 1:1, risk ratio of 2.31, and an odds ratio of 3. However, we did not reach our sample size, as only 17 HIV-exposed neonates were recruited. 149 neonates were recruited in order to increase the number of HIV-exposed neonates in the study, as not many HIV-exposed neonates were admitted to CN during the data collection period. Data on the sampled babies were collected using self-administered questionnaires, which were provided to the mothers. Data were analysed using Epi Info 3.5 software.

Ethical considerations

Ethical approval was granted by the College of Medicine Research and Ethics Committee (COMREC). Informed written consent was sought from the mothers of the neonates. Before consent was obtained, the mothers were assured of confidentiality. Study subjects were each assigned unique identification numbers.

Data collection

Once the mothers consented, details of the mother and baby were recorded on data collection forms. Babies had wrist bands on which their mothers' names were written. These wristbands were checked daily before taking any measurements from the babies.

Data management

Bilirubin levels were measured using a transcutaneous bilirubinometer, which was placed on the sternum and forehead of each baby, and the highest reading was recorded. Axillary temperatures were also measured using a thermometer. If a study subject's level of bilirubin was above the accepted treatment threshold, the investigators (three of whom were fourth-year medical students at the time of data collection) discussed the case with the doctor on duty for information about the treatment plan for the baby. The babies who developed jaundice were started on phototherapy. The measurements for temperature and bilirubin were taken every day for the duration of stay of the baby in CN. If pyrexia or changes in condition of the study patients was noted by the investigators, this information was immediately relayed to the clinicians responsible for patient care. Babies who developed jaundice, as well as those who did not, were monitored throughout their duration of stay in CN.

Data analysis

Microsoft Excel 2011 and Epi info 3.5 were used to record, store, and analyse the data that were collected.

Results

The total number of admitted neonates from 11 September 2013 to 9 October 2013 was 251. Of the 251 neonates admitted to CN, 149 neonates were recruited into the study. The prevalence of HIV among mothers giving birth at QECH was 13.8%. Sixty-one percent (91/149) of the neonates recruited into the study were males. Ten mothers (6.3%) who gave consent had not been tested for HIV, hence children born to these mothers were excluded from the study.

Table 2: Demographic characteristics of neonates born to HIV-positive and HIV-negative mothers

	HIV-positive n (%)	HIV-negative n (%)
Gender		
Male	10 (58.8)	81 (61.4)
Female	7 (41.2)	51 (38.6)
Gestational age		
Preterm (< 37wks)	10 (58.8)	46 (34.8)
Term (37 ≤ gestation ≤ 40)	7 (41.2)	86 (65.2)
Birth weight		
< 2500g	13 (76.5)	51 (38.6)
≥ 2500g	4 (23.5)	81 (61.4)
VDRL of mother		
Negative	2 (11.8)	16 (12.1)
Not tested	15 (88.2)	116 (87.9)
Mode of delivery		
SVD	12 (70.6)	67 (50.8)
CS	4 (23.5)	50 (37.9)
Other (e.g., breech, vacuum)	1 (5.9)	15 (11.4)

VDRL = Venereal Disease Research Laboratory (test)
SVD = Spontaneous vertex delivery
CS = Caesarean section

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Over 75% of neonates admitted to CN developed clinical jaundice (Table 3). Over half (64%) of the neonates with clinical jaundice were male, while the remainder (36.0%) were female. Gender was significantly associated with clinical jaundice (p = 0.033).

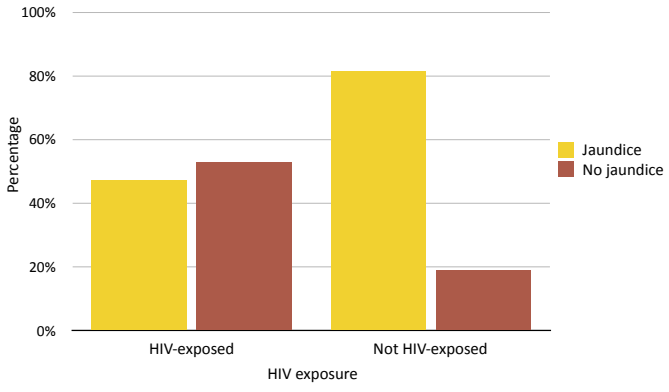
About 80% of neonates had low birth weight. Seventy percent of neonates with normal birth weight (birth weight ≥ 2500g) developed clinical jaundice. However, birth weight was not significantly associated with clinical jaundice (p = 0.140). About half of the HIV-exposed neonates and the majority (81%) of the HIV-non-exposed neonates developed clinical jaundice (Figure 1). HIV non-exposure was significantly associated with clinical jaundice (p < 0.001). Over 70% of full-term neonates and about 80% of preterm neonates developed clinical jaundice.

Table 3: Associations between clinical jaundice and demographic characteristics of study participants

	Clinical jaundice (> 5 mg/dL) n (%)	No jaundice	Chi-squared p-value
Gender			
Female	41 (70.7)	17 (29.3)	0.033
Male	73 (80.2)	18 (19.8)	
Gestational age			
Preterm (< 37 weeks)	47 (79.7)	12 (20.3)	0.753
Term (37 ≤ gestation ≤ 40)	65 (74.7)	22 (25.3)	
Birth weight			
< 2500 g	52 (81.3)	12 (18.8)	0.140
≥ 2500 g	61 (73.5)	22 (26.5)	
HIV status			
Exposed	8 (47.1)	9 (52.9)	< 0.001
Not exposed	107 (81.1)	25 (18.9)	
VDRL of mother			
Negative	14 (77.8)	4 (22.2)	0.969
Not tested	101 (77.1)	30 (22.9)	
Mode of delivery			
SVD	65 (82.3)	14 (17.7)	
CS	36 (66.7)	18 (33.3)	0.246
Other (eg., breech, vacuum)	14 (87.5)	2 (12.5)	

VDRL = Venereal Disease Research Laboratory (test)
SVD = Spontaneous vertex delivery
CS = Caesarean section

Figure 1: Incidence of clinical jaundice according to HIV exposure



Fifteen of the 17 HIV-exposed neonates were given nevirapine, as the mothers of two HIV-exposed neonates refused nevirapine prophylaxis. Both neonates who were not given nevirapine developed clinical jaundice. Six (40%) of the 15 neonates who were given nevirapine developed clinical jaundice.

The VDRL test was not performed on the majority of the mothers (88%). None of the mothers who were tested were VDRL-positive. Over 75% of neonates whose mothers were not tested (VDRL test) developed clinical jaundice.

Among neonates born via spontaneous vertex delivery (SVD), over 80% developed clinical jaundice. Over 60% of neonates born via caesarean section (CS) developed clinical jaundice. Almost all neonates (88%) born by alternative methods (breech or vacuum extraction) developed clinical jaundice. The mean bilirubin level for all neonates with and without HIV exposure peaked on day 4 (Figure 2).

Figure 2: Average bilirubin levels during the first 10 days of life

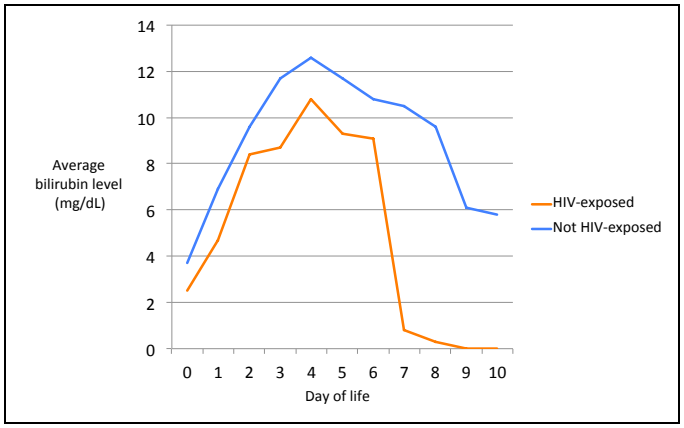
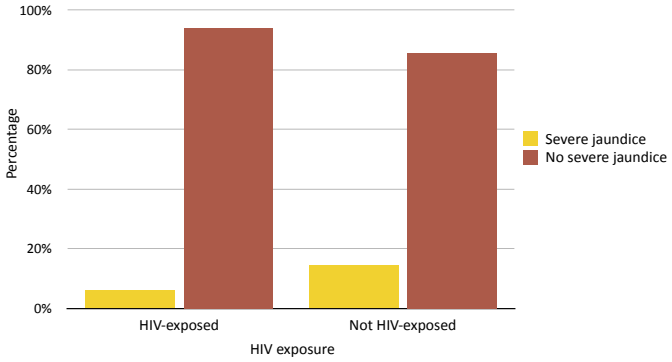


Figure 3: Incidence of severe jaundice according to HIV exposure



About 10% of the neonates developed severe jaundice and were put on phototherapy. Most of the neonates who developed severe jaundice were HIV-non-exposed (Figure 3). About 13% of neonates with low birth weights and 15% of neonates with normal birth weights developed severe jaundice. About 6% of HIV-exposed neonates and 14% of HIV-non-exposed neonates developed severe jaundice. Severe jaundice was not significantly associated with HIV exposure. About 12% of term neonates and 15% of preterm neonates developed severe jaundice. Sixteen (12.2%) of the 131 neonates whose mothers were not VDRL tested and 4 (22%) of the 18 neonates whose mothers were VDRL-negative developed severe jaundice. Nine (11.4%) of the 79 neonates born via SVD, nine (16.7%) of the 54 neonates born via CS and 2 (12.5%) of the 16 born by alternative methods (for example, breech or vacuum extraction) developed severe jaundice. Most neonates developed severe jaundice on day 3.

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The peak and fall in bilirubin levels was similar for both clinical and severe jaundice (Figure 4).

Adjusting for birth weight, mode of delivery, gestational age, gender and VDRL test, clinical jaundice was associated with HIV status ($p < 0.001$) (Table 5). Neonates with HIV exposure were 90% less likely to develop clinical jaundice than neonates without HIV exposure.

The odds of clinical jaundice are 2.6 times higher among male neonates than among female neonates when other factors are controlled for.

Controlling for birth weight, mode of delivery, gestational age, gender, and VDRL status, severe jaundice was not associated with HIV status ($p = 0.378$) (Table 6).

Table 4: Association between severe jaundice and demographic characteristics of study participants

	Severe jaundice n (%)	No severe jaundice	Chi-squared p-value
Gender			
Female	4 (6.9)	54 (93.1)	0.114
Male	16 (17.6)	75 (82.4)	
Gestational age			
Preterm (< 37 weeks)	9 (15.3)	50 (84.7)	0.432
Term (37 ≤ gestation ≤ 40)	11 (12.4)	78 (87.6)	
Birth weight			
< 2500 g	8 (12.5)	56 (87.5)	0.525
≥ 2500 g	12 (14.5)	71 (85.5)	
HIV status			
Exposed	1 (5.9)	16 (94.1)	0.378
Not exposed	19 (14.4)	113 (85.6)	
VDRL of mother			
Negative	4 (22.2)	14 (77.8)	0.333
Not tested	16 (12.2)	115 (87.8)	
Mode of delivery			
SVD	9 (11.4)	70 (88.6)	
CS	9 (16.7)	45 (83.3)	0.961
Other (eg., breech, vacuum)	2 (12.5)	14 (87.5)	

VDRL = Venereal Disease Research Laboratory (test)
SVD = Spontaneous vertex delivery
CS = Caesarean section

Figure 4: Daily bilirubin levels in neonates with severe and clinical neonatal jaundice

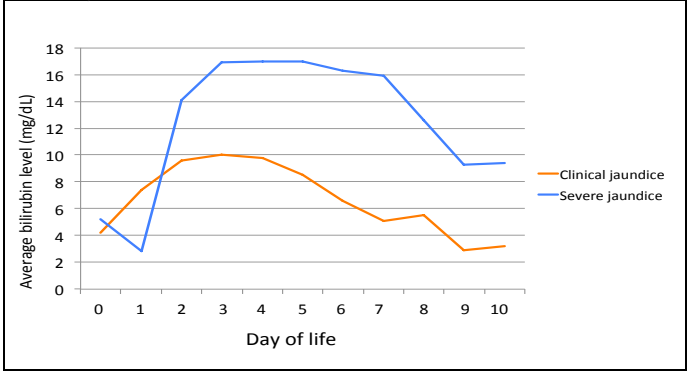

Table 5: Estimated odds ratios from the logistic regression model for clinical jaundice and several predictor variables

Variable	Odds ratio	95% CI for odds ratio	p-value
Birth weight	0.32	0.07 – 1.46	0.140
Caesarean section	0.34	0.07 – 1.63	0.175
Gestational age	1.27	0.29 – 5.47	0.753
Gender	2.62	1.08 – 6.37	0.033
HIV status	0.10	0.03 – 0.35	p < 0.001
SVD	1.19	0.24 – 5.83	0.834
VDRL status	0.97	0.26 – 3.68	0.969

SVD = Spontaneous vertex delivery
VDRL = Venereal Disease Research Laboratory (test)

Table 6: Estimated odds ratios from the logistic regression model for severe jaundice and several predictor variables

Variable	Odds ratio	95% CI for odds ratio	p-value
Birth weight	1.72	0.32 – 9.11	0.525
Caesarean section	1.37	0.25 – 7.48	0.714
Gestational age	0.52	0.10 – 2.67	0.432
Gender	2.59	0.80 – 8.42	0.114
HIV status	0.38	0.05 – 3.22	0.378
SVD	1.14	0.20 – 6.41	0.880
VDRL status	1.90	0.52 – 7.01	0.333

SVD = Spontaneous vertex delivery
VDRL = Venereal Disease Research Laboratory (test)

Discussion

Our study showed a strong negative association between the incidence of clinical jaundice and HIV exposure. Contrary to our initial hypothesis, the incidence of neonatal jaundice at CN was less in the HIV-exposed than in the HIV-non-exposed group. There was no association between HIV exposure and severe jaundice.

Studies have found high rates of prematurity, low birth weight, and very low birth weight in the infants of HIV-positive mothers.[8,9] Notably, prematurity and low birth weight are risk factors that predispose HIV-exposed neonates to develop jaundice. The incidence of neonatal jaundice at CN was, however, less in the HIV-exposed than in the HIV non-exposed babies, and several explanations could be suggested for the results obtained.

First, it could be because of the relatively small sample size of the study. There were fewer HIV-exposed neonates admitted to CN than we initially expected. This could be because most HIV-exposed neonates who were born at QECH did not meet the criteria to be admitted to CN. Consequently, the number of HIV-exposed neonates was small and this affected our statistical analysis. The results cannot be generalised to the population.

Additionally, many of the HIV-exposed neonates who were admitted to CN were of low birth weight and premature, did not have other co-morbidities and were discharged within two days after admission. Bilirubin levels generally peaked on days 3 and 4 (Figure 2), but since most HIV-exposed neonates stayed at CN for less than 2 days, the results show

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that they did not develop jaundice. However, these HIV-exposed neonates might have developed jaundice after discharge and presented to health centres elsewhere.

Furthermore, controlling for confounders using logistic regression, gender and maternal HIV status were negatively and significantly associated with clinical jaundice. This agrees with previous research done elsewhere, which showed that male gender is a known risk factor for pathological jaundice.[13] Birth weight, gestational age, and mode of delivery were not significantly associated with jaundice.

A possible hypothesis as to why HIV-exposed neonates were less likely to develop jaundice, at least in the initial days of life, might be related to the Malawi's current PMTCT protocol. The national PMTCT guidelines stipulate that all HIV-seroreactive pregnant and breastfeeding women should be started on an antiretroviral therapy regimen that contains efavirenz (along with tenofovir and lamivudine). The efavirenz may act as a foetal liver enzyme inducer, and this would help in the conjugation of bilirubin, resulting in HIV-exposed neonates having less serum bilirubin levels than their HIV-non-exposed counterparts.

Limitations

The study used a non-invasive technique (transcutaneous bilirubinometer) for measuring the bilirubin levels. These devices are not always accurate, especially if the neonate has been placed under phototherapy. Using the gold standard—serum birubin level measurement—would have been more ideal.

The number of neonates who developed jaundice could be higher than that found in this study because most neonates developed jaundice after being discharged from the ward, and this depended on the mothers noticing that their child was looking yellowish.

Lastly, The sample size for HIV-exposed infants was not reached, as we recruited only 17 of the calculated 69 neonates. The study period could have been increased, or the study field could have been extended to other health facilities in order to have had a larger sample size. With a larger sample size, our results could have, at least, approached generalisability on a national level.

Conclusions

This short cohort study showed that, in young neonates, jaundice was less common in HIV-exposed babies despite the use of nevirapine. Although this is reassuring, a larger study with longer follow-up is needed.

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